being used as initial treatment for symptomatic Parkinson's disease and can delay the need for levodopa by one or more years. As monotherapy, pramipexole and ropinirole are largely devoid of the adverse effects that frequently complicate treatment with levodopa, namely motor fluctuations (in the most severe form known as "on-off") and dyskinesia (involuntary choreic movements). Pramipexole and ropinirole are also used with levodopa in more advanced patients to prolong the response to each dose of levodopa and to reduce the trough severity of parkinsonism. Both new agonists are well tolerated but can have adverse effects that resemble those of other dopaminergic agents, such as nausea, dizziness, orthostatic hypotension, confusion, and hallucinations. In conjunction with levodopa, they can cause dyskinesia. Because pramipexole and ropinirole are not ergot derivatives, they may lack rare adverse effects such as retroperitoneal and pulmonary fibrosis associated with the older dopamine agonists. Direct comparisons among the new and old dopamine agonists are scant, but some studies suggest that ropinirole and pramipexole may be superior to bromocriptine.

Tolcapone and entacapone, inhibitors of catechol-O-methyl transferase (COMT), will be introduced in the near future; Tolcapone is FDA approved. These drugs block O-methylation of levodopa to an inert compound, thereby slowing clearance of levodopa from plasma and increasing the amount of levodopa entering the brain, which enhances the response to levodopa. Their effect is somewhat like controlled-release levodopa. The COMT inhibitors have no clinical effect unless they are combined with levodopa. The side effects of tolcapone and entacapone alone are diarrhea. In combination with levodopa, the adverse effects are the same as those of excessive levodopa, so it is often necessary to reduce the levodopa dose.

Protective therapies to slow the degeneration of dopaminergic neurons remain at the forefront of scientists' and clinicians' minds. Selegiline, a selective, irreversible MAO-B inhibitor, was widely adopted following the Parkinson's Study Group report that it delayed the need to start levodopa by over a year. The initial enthusiasm for selegiline has been tempered by the recognition that selegiline can reduce or reverse symptoms but not necessarily affect the progression of the disease. So although selegiline's symptomatic actions can contribute to the delay in need for levodopa, it does not clearly alter progression of the disease once levodopa is started. A large British study suggested that selegiline increased mortality rates, but this finding has not been replicated. Thus, the protective actions of selegiline are controversial. In current clinical practice, selegiline is more commonly used in patients early in the disease and withdrawn later in the course when patients are on multiple antiparkinsonian drugs. It can cause confusion, dyskinesia, orthostatic hypotension, and nausea. Despite the uncertainties that surround selegiline, the search for protective therapies continues with investigations of agents to reduce free-radical formation and damage in the basal ganglia, of glutamate antagonists to reduce excitotoxicity, and of mitochondrial electron chain cofactors to enhance neuronal energy production.

Thalamotomy is increasingly used for disabling rest or postural tremor that is unresponsive to pharmacological management. Unilateral thalamotomies abolish or greatly reduce contralateral tremor but do not affect the other parkinsonian signs of rigidity and bradykinesia. Bilateral procedures are associated with a high incidence of dysarthria, dysphagia, and disequilibrium, and they are only reluctantly used in severely affected patients. A new approach is to implant stimulating electrodes in the thalamus, because high-frequency stimulation will inactivate neurons in the vicinity of the electrode tip and produce a reversible thalamotomy. Adverse effects can be minimized by altering the stimulation parameters, and bilateral procedures can be done without the concern of irreversible dysarthria, dysphagia, and disequilibrium. The drawbacks are the expense of the stimulator, the periodic need for battery replacement, and the considerable effort required to find the optimal stimulation parameters. A common compromise is to do a thalamotomy on the first side and, if needed, thalamic stimulation on the contralateral side at a later date. Pallidotomy ameliorates contralateral levodopa-induced dyskinesia. It may also improve other aspects of parkinsonism, but severe dyskinesia is the major indication for the procedure. The adverse effects of bilateral pallidotomies are similar to those of bilateral thalamotomies and are therefore rarely performed. Unilateral and bilateral stimulation of the pallidum and subthalamic nucleus are promising, safer techniques that are under intense investigation for treatment of parkinsonism.

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Recent Advances in the Treatment of Neuropathies

THERE IS A GROWING arsenal of immunomodulating therapies—including glucocorticoids, immunosuppressant drugs, intravenous immune globulin (IVIg), and plasmapheresis—that is used to treat peripheral neuropathies. These therapies control underlying immune processes that attack nerves. Recovery from dysimmune neuropathies, however, requires more than the control of underlying immune processes. It also requires repair and recovery of peripheral nerve that no therapy has been shown to enhance or alter. In axonal neuropathies, the goal is stabilization of function, because recovery follows axon regeneration and collateral reinnervation. This takes years and is incomplete. In demyelinating

neuropathies, the goal is restoration of function, because recovery follows remyelination. This takes only months and is complete. Once full benefit is achieved, whether stabilization or restoration, therapy should be reduced—it is toxic or costly. Therapy reduction requires close surveillance for clinical relapse, which would indicate that control over underlying immune processes attacking nerve has been lost.

Over a decade ago, French and North American studies demonstrated that acute idiopathic demyelinating neuropathy, Guillain Barre syndrome (GBS), can be treated with plasmapheresis. A recent follow-up study found doses can be adjusted to severity without losing benefit: 2 plasma exchanges in mild GBS and no more than 4 plasma exchanges in moderate and severe GBS. The Dutch have found that IVIg is as effective as plasmapheresis. Plasmapheresis requires special equipment available at special centers, whereas IVIg is widely available. Plasmapheresis may cause hypotension and malaise; IVIg causes fever, headache, myalgia, rash, anaphylactic reaction, thromboses, infarcts, congestive heart failure, and hepatitis C. The frequency of side effects is similar between the treatments. Both cost about $6,000 to $12,000 for 4 to 6 treatments. The cost is not trivial, but it is justified by the savings that comes from reduced hospitalization, morbidity, and disability.

Traditionally, chronic idiopathic demyelinating neuropathy has been treated with large glucocorticoid doses (prednisone, 1 to 2 mg per kg of body weight a day, up to 100 mg a day). There is a growing tendency to use other immunomodulatory therapies alone or in various combinations as alternatives or as adjuncts to glucocorticoids. Plasmapheresis and IVIg are effective in controlling disease. Maintenance therapy every 4 to 6 weeks is usually necessary. Azathiaprine, cyclophosphamide (in oral daily doses or monthly intravenous pulses), and cyclosporin A are increasingly used as adjunct, steroid-sparing therapy, as alternatives to glucocorticoid therapy, or as second-line therapy. Eradication rather than mere control of disease is achievable in some patients. No well-conducted trial has compared these therapies directly. Drug therapy takes months before seeing its benefit, so combining modalities is sensible. Therapy is often started with plasmapheresis or IVIg for early reversal of deficits and maintained with drugs for long-term control (if not eradication).

Multifocal motor neuropathy may represent a variant of chronic idiopathic demyelinating polyneuropathy. It starts with progressive, asymmetric, pure, or mostly pure motor weakness, atrophy, and fasciculations and resembles motor neuron disease, for which it is occasionally tragically mistaken. It is caused by immune-mediated focal demyelination in peripheral nerves, which leads to conduction blocks. An association with antibody to GM1 ganglioside, initially believed to be hallmark, is now known to be inexact—probably only 50% of patients have the antibody. Treatment is usually gratifying with IVIg; most patients depend on treatment every 4 to 6 weeks. If treatments begin to fail, either dose or frequency of IVIg may be increased or other immunomodulating therapies, especially cyclophosphamide, may be invoked.

The association between neuropathy and paraproteinemia has been appreciated for over a decade. Ten percent of patients with neuropathy have a monoclonal gammopathy (as opposed to 0.1% to 3.0% of the general population) and nearly 50% of gammopathy patients have neuropathy. But despite intense interest, the correlation of clinical syndrome and paraproteinemic syndrome remains unclear. Antibodies to various peripheral nerve antigens including myelin associated glycoprotein (MAG), sulfatide, GM1, asialo-GM1, and GD1b can be detected, but doing so has dubious value for classifying the neuropathy and determining the course of therapy. Therefore, these determinations they have a limited role. Therapy should be directed at the cause of the paraproteinemic syndrome, such as myeloma, plasmacytoma, lymphoma, or amyloidosis. If the cause of the paraproteinemia is established, so-called monoclonal gammopathy of undetermined significance, therapy of the neuropathy should depend on clinical circumstances and pathophysiolgy. Immunomodulating therapy should be used for demyelinating neuropathies; cautious (if any) therapy should be used for axonal neuropathies because treatment may be ineffective and hazardous and have a benefit that is difficult to monitor.

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Endovascular Treatment of Vasospasm

CEREBRAL VASOSPASM IS A serious complication facing patients with aneurysmal subarachnoid hemorrhage (SAH) and is the leading cause of death and disability in this group. Because vasospasm is a delayed phenomenon, its occurance can lead to a poor outcome despite a technically successful early aneurysm clipping. Identifying vasospasm is based on symptoms, with confirmation by diagnostic testing. Transcranial doppler (TCD) is a bedside, noninvasive technique, but it suffers from problems with sensitivity and specificity, operator dependence, and inconsistent visualization. Cerebral angiography, the gold standard for the detection of vasospasm, is invasive and carries a small, but real, risk of vessel injury, stroke, or death.